Mechanisms Of DEMentia - Longitudinal Amyloid-beta Measurements and Blood-brain barrier Dysfunction in Alzheimer and CAA

Published: 22-07-2024
Last updated: 27-12-2024

Primary objective: describe the longitudinal changes of Aβ38, Aβ40, Aβ42, and Aβ43 concentrations in CSF of patients with CAA, AD, and healthy control cases and estimate the differences in change between those…

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56900

Source
ToetsingOnline

Brief title
MODEM-LAMBDA-C

Condition

- Other condition
- Cranial nerve disorders (excl neoplasms)
- Vascular haemorrhagic disorders

Synonym
Alzheimer dementia, Alzheimer's disease, Cerebral amyloid angiopathy

Health condition

Dementie

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW - MODem project consortium

Intervention

Keyword: Alzheimer's disease, Amyloid-beta, Cerebral amyloid angiopathy, Cerebrospinal fluid

Outcome measures

Primary outcome

Primary objective:

Describe the longitudinal changes of Aβ38, Aβ40, Aβ42, and Aβ43 concentrations

in CSF of patients with CAA, AD, and healthy control cases and estimate the

differences in change between those groups.

Secondary outcome

1. Quantified volume of cerebral perivascular gadolinium signal and structural

features in CAA patients

2. Biomarker assays for BBB-dysfunction detection

3. Correlations between biomarker concentrations with Aβ in the study

populations

4. Correlation between biomarker concentrations and gadolinium signal

5. Correlation analysis between APOE and BBB-dysfunction biomarker and the Aβ

peptides

Study description

Background summary

We have recently described that different forms of the amyloid beta peptide, Aβ38, Aβ40, Aβ42, and Aβ43, have different concentrations in cerebrospinal fluid (CSF) when cross-sectionally compared between (Dutch-type) Cerebral amyloid angiopathy ((D-)CAA), Alzheimer*s disease (AD), and healthy control patients (de kort, et. al. 2022). These peptides and other toxic molecules are cleared from the brain by the blood brain barrier (BBB). Despite being studied extensively at a single time point, the temporal changes in concentrations is currently unknown in both the pathophysiological and physiological context. Furthermore, it is unclear if concentration changes are correlated with the dysfunction of the BBB due to the lack of adequate BBB-monitoring biomarkers.

Describing the longitudinal changes of amyloid-beta in CSF of CAA and AD patients will provide additional insights in the mechanisms of these neurodegenerative diseases. Moreover, early stage changes of concentraties could function as earlie stage diagnostic tool for CAA and/or AD. This is benefitial with the prospect of novel treatments targeting amyloid-beta. Furthermore, monitoring these peptides overtime during disease can be used as additional prognostic biomarker.

Describing BBB-dysfunction with the use of biomarkers has potential to elucidate the ethiology and progressive character of CAA, AD and potentially other neurodegenerative diseases. In addition, these biomarker could play an assisting role in therapydesicion or early detection of intracerebral heamorraghes.

Study objective

Primary objective: describe the longitudinal changes of Aβ38, Aβ40, Aβ42, and Aβ43 concentrations in CSF of patients with CAA, AD, and healthy control cases and estimate the differences in change between those groups.

1. Explorative study to establish brain (micro)structure and vascular function measured with MRI in the CAA and control study populations.
2. Develop robust assays for quantification of novel CSF and blood biomarkers indicating BBB impairment.
3. Explorative cross-sectional study to describe if the Aβ peptide concentrations correlate with the measured BBB-dysfunction biomarkers and if these correlations differ between the study populations.
4. Explorative cross-sectional study to describe if the Aβ peptide and BBB-dysfunction biomarker concentrations correlate with BBB-dysfunction measured with DCE-MRI in the CAA and control study populations.

5. Explorative cross-sectional study to describe if the variants in the APOE gene have a correlation with the measured Aβ peptides and BBB-dysfunction biomarker(s).

Study design

Longitudinal cohort study with at least two years interval.

Study burden and risks

Patiënts are asked to undergo a lumbal puncture, venipuncture, and a cognitive test.

A part of the studypopulation, those who participated in either the BIONIC or CAFE study, will be invited one visit. For this population the baseline visit was during these studies and therefore the second visit is scheduled. Therefore, these participants will only undergo above mentioned procedures once.
The participants who had not participated in the BIONIC or CAFE study will be asked to visit twice with an interval of two years. The participant will under go above mentioned procedures once at both the baseline visit and at the second visit.

For the lumbar puncture the participant is asked to lie sideways with knees towards the chest, similar to the feutus position. Next, the medical professional will puncture the lowerback, here is a sack located containing cerebrospinal fluid. Damaging of the spinal cord is avoided by performing the puncture at this position at the lowerback since there is no spical cord located here.
Some people develop post-puncture headaches. Most often do these complains subside when the participants lies down. For a small percentage these headaches could occure for several days. This occurs for approxemately 4% of the patients when using an atraumatic needle. To reduce the chance of headache development; a 20-gauge neelde is used as well. In addition, the participant is adviced to consume caffein containing drinks in addition to drinking a proper amount of water. The occurance of a heamorage or infection is extemely rare (<0.1%). To minimize the occurance are both the skin and materials desinfected.
The skin around the puncture site is temporately and locally numbed to reduce discomfort of the participant.

During the venipuncture a vene in the anterior of the elbow is used to obtain blood. This is routinely performed by the medical professional and the risks are negligible.

The cognitive test in this study is the Dutch equivalent of the MoCA test. The duration of this test is around 10 minutes.

The observed side-effects of Gadovist administration are: headache, nausea, injection site reactions, disturbed sense of taste and hot feeling (from >= 1/1000 to < 1/100 cases).

The overall risk of this study is estimated as "negligible".

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with CAA:
To be eligible to participate, a subject must meet the following criteria:
1) Fulfilment of the Boston criteria 2.0 for CAA;
2) Subjects are mentally competent to take a decision on participation;

3) Most recent ICH was at least 6 months ago;
4) Age >50 years;
5) Written informed consent;
6) If participant participated in the BIONIC/CAFÉ study: Lumbar puncture at baseline visit successfully acquired CSF.

Patients with AD:
To be eligible to participate, a subject must meet the following criteria:
1) Fulfilment of the NIA-AA criteria for probable AD.
2) Subjects are mentally competent to take a decision on participation;
3) Written informed consent;
4) Age >50 years;
5) If participant participated in the BIONIC/CAFÉ study: Lumbar puncture at baseline visit successfully acquired CSF.

Control cases:
To be eligible to participate, a subject must meet the following criteria:
1) Age >50 years;
2) A MoCA score >=27
3) Subjects are mentally competent to take a decision on participation;
4) Written informed consent

Exclusion criteria

Exclusion CAA:
1) Presence of blood coagulopathy, established by medical history;
2) History of major psychiatric disorder;
3) Pregnancy at time of study participation;
4) Allergy to local anesthetic agents;
5) Contra-indication for lumbar puncture: medical history of compression of spinal cord, spinal surgery, skin infection, developmental abnormalities in lower spine;
6) Subjects who are currently participating in another study or have participated in a clinical study within the previous 30 days, based on their own report;
7) Subjects with a history or current drug or alcohol abuse;
8) Subjects who are part of the study staff personnel or family members of the study staff personnel.
9) Proven mutation carrier for the D-CAA (tested only on clinical indication)
10) Contra-indications for MRI

Exlcusion AD:
1) Presence of blood coagulopathy, confirmed by medical history;

2) History of major psychiatric disorder;
3) Pregnancy at time of study participation
4) Allergy to local anesthetic agents;
5) Contra-indication for lumbar puncture: medical history of compression of spinal cord, spinal surgery, skin infection, developmental abnormalities in lower spine;
6) Subjects who are currently participating in another study or have participated in a clinical study within the previous 30 days, based on their own report ;
7) Subjects with a history or current drug or alcohol abuse;
8) Proven mutation carrier for a gene known to be associated with early-onset hereditary AD (tested only on clinical indication)
9) Subjects who are part of the study staff personnel or family members of the study staff personnel.

Exclusion control cases:
1) Self-reported (subjective) cognitive decline;
2) History of major neurological (e.g. stroke, neurodegenerative disease, brain tumours, brain infection or inflammation) or psychiatric disorder;
3) Pregnancy at time of study participation
4) Presence of blood coagulopathy, confirmed by medical history;
5) Allergy to local anesthetic agents;
6) Contra-indication for lumbar puncture: medical history of compression of spinal cord, spinal surgery, skin infection, developmental abnormalities in lower spine;
7) Subjects who are currently participating in another study or have participated in a clinical study within the previous 30 days, based on their own report ;
8) Subjects with a history or current drug or alcohol abuse;
9) Proven mutation carrier for a gene known to be associated with early-onset hereditary AD (tested only on clinical indication) or D-CAA
10) Subjects who are part of the study staff personnel or family members of the study staff personnel.
11) Contra-indications for MRI

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2024
Enrollment:	90
Type:	Anticipated

Ethics review

Approved WMO

Date:	22-07-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85709.091.23